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Efficacy and safety of Chimeric Antigen Receptor T-cell (CAR-T) therapy in patients with hematologic and solid malignancies: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: Patients with relapsed or refractory malignancies have a poor prognosis. Immunotherapy with Chimeric Antigen Receptor T (CAR-T) cells redirects a patient's immune cells against tumor antigen. CAR-T cell therapy has demonstrated promise in treating patients with several hematologic malignancies, including acute B cell lymphoblastic leukemia and B cell lymphomas. CAR-T cell therapy for patients with other solid tumors is also being tested. Safety is an important consideration in CAR-T cell therapy given the potential for serious adverse events, including death. Previous reviews on CAR-T cell therapy have been limited in scope and methodology. Herein we present a protocol for a systematic review to identify CAR-T cell interventional studies and examine the safety and efficacy of this therapy in patients with hematology malignancies and solid tumors.

Methods and analysis: We will search MEDLINE, including In-Process and Epub Ahead of Print, EMBASE, and the Cochrane Central Register of Controlled Trials. Studies will be screened by title, abstract, and full text independently and in duplicate. Studies that report administering CAR-T of any chimeric antigen receptor construct targeting antigens in patients with hematologic malignancies and solid tumors will be eligible for inclusion. Outcomes to be extracted will include complete response rate (primary outcome), overall response rate, overall survival, relapse, and adverse events. A meta-analysis will be performed to synthesize the prevalence of outcomes reported as proportions with 95% confidence intervals. The potential for bias within included studies will be assessed using a modified Institute of Health Economics tool. Heterogeneity of effect sizes will be determined using the Cochrane I^2 statistic.

Ethics and Dissemination: The review findings will be submitted for peer-reviewed journal

publication and presented at relevant conferences and scientific meetings to promote knowledge transfer.

Registration: The protocol has been registered with the International Prospective Register of Systematic Reviews (Awaiting registration number).

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STRENGTHS AND LIMITATIONS OF THIS STUDY

1. Our review will provide a comprehensive synthesis of the current literature and be the first review of trials investigating chimeric antigen receptor T (CAR-T) cell therapy among patients with solid tumors.
2. A major methodological limitation is that all eligible studies are expected to be single arm and have no comparator group. This may increase risk of bias when interpreting results.
3. We provide a comprehensive plan to address limitations of meta-analysis of single arm studies that includes use a modified Institute of Health Economics tool for assessing risk of bias in single arm interventional studies. Our approach can serve as a model for future systematic reviews assessing early-phase clinical data that is often single arm with no control comparison.

INTRODUCTION

Among patients with relapsed and refractory malignancies, chimeric antigen receptor T (CAR-T) cell therapy is a novel immunotherapy that has shown promise in both pre-clinical and early clinical studies. This therapy allows for CARs directed against tumour associated antigens (e.g. CD19, HER-2) to be introduced into a patient's T cells; this serves to reprogram these cells to target the patient's tumor cells. A number of small clinical trials using anti-CD19 CAR-T cells in

hematologic malignancies have demonstrated sustained responses in patients with advanced disease [1-5]. CAR-T cell therapy for solid malignancies has also identified a number of potential cancer-specific targets and previous pre-clinical studies investigating efficacy and feasibility show promise [6].

In spite of some evidence of efficacy of CAR-T cell therapy against some malignancies, there are a number of safety concerns that have been identified. Trials conducted by Juno Therapeutics and Kite Pharma reported mortality among patients with hematologic malignancy treated with CAR-T cell therapy [7, 8]. The Juno Therapeutics trial was closed after the death of five patients from cerebral edema linked to CAR-T cell therapy [9]. Previous trials investigating CAR-T cell therapy among patients with solid tumors have reported adverse events from treatment including anaphylaxis and cardiac arrest [10]. Past studies have also reported other challenges in applying CAR-T cell therapy to solid tumors, including a scarcity of tumor associated antigen targets, the potent immunosuppressive effects of the tumor microenvironment, and the limited trafficking of CAR-T cells to tumor sites [11, 12].

Due to the variability and small size of clinical trials investigating CAR-T therapy there is a need for a systematic review to evaluate its efficacy and safety. Although no systematic review currently exists for CAR-T therapy among solid tumors, we have identified four publications that self-identified as systematic reviews studying the efficacy and safety of CAR-T therapy for patients with hematologic malignancies [13, 14-16]. However, there were significant limitations in the scope and/or methodologies in these earlier reviews. Zhu *et al.* only considered CD19 targeted CAR-T therapies, did not report differences between adult and pediatric populations,

and employed a non-systematic search strategy [14]. Anwer *et al.* only included allogeneic T-cells, whereas most CAR-T cell therapy uses autologous cells [15]. Another systematic review by Zhang *et al.* only considered CD19 CAR-T therapies and was published in journal controlled by a predatory publisher [13, 17]. Finally, while titled as a systematic review, Holzinger *et al.* is only a narrative review [16]. Given these limitations of previous publications, along with rapid evolution of the CAR-T field, there is a need for a current systematic review, as we present here, that adheres to rigorous, state-of-the-art methods and summarizes the findings among both solid tumors and hematologic malignancies.

Our systematic review will clarify the determinants of efficacy and safety of CAR-T therapy and identify gaps in current practice and knowledge. This will also be the first review to investigate CAR-T therapy among patients with solid tumors. We expect the results from this clinical systematic review will help inform the design of clinical trials. We also summarize our approach to appraise and analyze single arm interventional studies that are typically conducted for early phase biotherapeutic trials; we believe this approach may be replicated for other systematic reviews of early phase clinical data.

Protocol

Our review protocol is reported in accordance with the Preferred Reporting Items in Systematic reviews and Meta-Analysis-Protocol guidelines (see supplemental research checklist) [18].

Research objectives

We will review controlled and uncontrolled interventional studies of CAR-T cell therapy to examine the safety and efficacy of this treatment in patients with relapsed or refractory hematological malignancies and solid tumors.

METHODS AND ANALYSIS

Eligibility criteria

Studies will be selected according to the eligibility criteria detailed in Table 1. Interventional studies with and without comparators will be included. We anticipate that many of the included studies will be single-arm interventional studies. Full text articles in any language will be considered. Unpublished gray literature, abstracts, commentaries, letters, reviews, and editorials will be excluded [19].

Table 1. Population, Intervention, Comparison, Outcome, and Study design breakdown of study eligibility criteria

Category	Description of criteria
Population	Patients with solid tumor or hematologic malignancies
Intervention	Chimeric antigen receptor T cell therapy
Comparator(s)	Studies with or without any comparator will be considered
Outcome(s)	Primary outcome: • Complete response Secondary outcomes: • Overall response (hematological) or objective response (solid) • Progressive disease • Relapse • Overall survival • Adverse events (infection, neurotoxicity, cytokine release syndrome, B-cell aplasia, graft versus host disease, other types will be grouped by organ system affected and severity) Tertiary outcomes: • Health-related quality of life • Health utility measures • Patient experience
Study design	Interventional: +/- controlled, +/- randomized

Information sources

We will search MEDLINE (OVID interface, including In-Process and Epub Ahead of Print), EMBASE (OVID interface), and the Cochrane Central Register of Controlled Trials (Wiley interface). Clinical trial registries will be searched to identify ongoing and completed trials. Specifically, ClinicalTrials.gov and the International Prospective Register of Systematic Reviews will be searched to identify ongoing or recently completed trials or systematic reviews. In order to further ensure a comprehensive literature search, we will examine reference lists of included studies or relevant reviews identified through the search. We will also contact key researchers in the field of CAR-T to ensure relevant studies have been identified. Finally, we will circulate a bibliography of included articles to the systematic review team for feedback.

Search strategy

Specific search strategies will be created in collaboration with a Health Sciences Librarian (RS) with expertise in the design of systematic searches. The literature search strategies will be developed using key words related to CAR-T cell therapy as well as hematological malignancies and solid tumors. Search strategies will use controlled vocabulary (e.g. Receptors, Antigen, T-Cell) and keywords (e.g. CAR-T). The syntax and subject headings used in the finalized EMBASE strategy will be adapted to the other databases. A validated search filter for clinical studies will be applied. Both qualitative and quantitative studies will be sought. No study design, date or language limits will be imposed on the search. A Peer Review of Electronic Search Strategy will be performed by a second librarian who is not associated with the project [20]. A draft of the Medline (OVID interface) search strategy for hematologic and solid tumors is shown in supplemental appendix 1.

Study records

The literature search results will be uploaded to Distiller Systematic Review Software (DistillerSR®, Evidence Partners, Ottawa). DistillerSR is a cloud-based software program that provides transparent, reproducible, and audit-ready results necessary for accurate review.

Data collection process

Two review authors (EG, ML) will independently screen the titles and abstracts from the search results using the pre-defined inclusion criteria presented in Table 1. A calibration test will be performed to refine the screening question prior to formally commencing the screening process. For all titles that appear to meet the inclusion criteria or where there is any uncertainty, we will access the full text. Two review authors (EG, FH) will assess the eligibility of full reports. Disagreement will be resolved through discussion with a third party member (DF, HA, ML, NK). We will record the reasons for excluding studies.

Data items

Standardized drafts of data extraction forms were designed to extract all information of interest from the screened studies in adherence with the Effective Practice and Organisation of Care guidelines [21]. The drafts will be used to inform the construction of the online data abstraction program (DistillerSR). Data will be extracted independently and in duplicate from each eligible study (EG, FH). A calibration exercise will be conducted prior to formally starting data abstraction. Demographic information, methodology, intervention details, and outcomes will be recorded. Reviewers will resolve disagreements by discussion or by conferring with one of two

arbitrators (ML, DF), who will adjudicate to resolve disagreements. Where uncertainty is identified, we will contact study authors for more information.

Study characteristics to be extracted will include the journal title, the first author, the inclusion criteria (outlined in Table 1), patient characteristics (mean age, sex, malignancy diagnosis), trial design, type and source of financial support, publication status from trial reports, and study sample size. Study intervention characteristics to be extracted will include lymphodepletion method (preconditioning agents), previous treatment (ablative, non-ablative), failed transplant, co-morbidities, concomitant medications, and length of follow-up. CAR-T intervention characteristics to be extracted will detail manufacturing and cell product characteristics, including: fresh or frozen, T-cell origin, selection of T cell subsets, T cell expansion method including cell culture duration, CAR target antigen, CAR antigen, CAR molecular structure (i.e. affinity domain, hinge domain, transmembrane domain, co-stimulatory domain(s), signaling domain), transfection/transduction method, and the therapeutic regimen (CAR-T dose, frequency, duration, route of administration). Absolute lymphocyte counts prior to CAR-T cell therapy administration will also be recorded as this has useful information for patient eligibility of CAR-T cells. Among solid tumors, the tumour regression grade will be reported when available. When necessary, we will obtain measures of central tendency and dispersion of data by analyzing the figures and tables or by contacting the authors. Whenever possible, the results from an intention to treat analysis will be used.

Outcome justification and prioritization

Primary outcome

Complete response, our primary outcome, will be defined by type of disease: hematological malignancies acute lymphocytic leukemia (ALL) or acute myeloid leukemia (AML) and solid tumors. If complete response is not feasible, secondary response outcomes will be reported using best overall response when available. Best overall response will be defined according to the response evaluation criteria in solid tumors (RECIST) guidelines where patients will be assigned into one of the following categories: Complete response, partial response, stable disease, progression, or inevaluable for response [22]. Studies that recruit patients in complete remission at the initiation of CAR-T cell therapy will not be included in the complete response data reported.

ALL and AML

For patients with ALL or AML, in studies that: 1) do not provide a definition for complete response, it will be considered hematologic response; 2) report minimal residual disease, response will be defined as molecular response. The sensitivity of the assay used will also be extracted for molecular response.

Solid tumors

For patients with solid tumors, target lesion and non-target lesion complete responses will be defined as disappearance of all target lesions and non-target lesions, respectively, where non-target lesions must be accompanies by normalization of tumor marker level as defined by RECIST guidelines [22]. In patients with solid tumors, any pathological lymph nodes (among target or non-target lesions) must decrease in the short axis to less than 10mm [22]. Furthermore,

in studies that report tumor regression grading of zero, response will be defined as pathological response.

Secondary outcomes

Overall response, progression of disease, relapse, and adverse events are our secondary response outcomes to be measured.

Overall response or objective response

Overall response and objective response will be defined as the sum of partial or complete responses in both hematologic malignancies and solid tumors, respectively. In hematologic malignancies, partial response is considered when there has been a response to therapy but does not meet the criteria for complete response. In target lesion evaluation for solid tumors, partial response is defined as a 30% decrease in the sum of target lesion diameters (compared to baseline measures) [22].

Progressive disease

Progressive disease in hematologic malignancies is considered when evidence of disease increases in the peripheral blood or bone marrow, or progression or new extramedullary disease is identified. In solid tumors progressive disease is defined as a relative increase in the sum of target lesions by 20% (smallest sum as reference), an absolute increase in target lesions by 5 mm, as well as appearance of any new lesions [22]. In both hematologic and solid tumors, stable disease is defined as not meeting criteria for partial response, complete response or progression.

Relapse

Relapse is defined as a patient who has a partial or complete response but then develops disease progression. Studies that recruit patients in complete remission at the initiation of CAR-T cell therapy will be descriptively reported in the proportion of the patients that relapse. For patients

with lymphoma or chronic lymphocytic leukemia (CLL), response criteria are defined as per the RECIST guidelines [22]. Lastly, if CLL is identified as circulating disease in the peripheral blood and/or bone marrow only, the response criteria that is used for AML and ALL will be employed.

Adverse events

Adverse events secondary outcomes will be used to evaluate clinical safety of CAR-T cell therapy. Adverse events are a measure of unplanned or undesired symptoms or diagnoses that occur during the study, which were absent at baseline, or worsen over the course of the study [25]. In the setting of CAR-T cells, adverse events of special interest include infection, neurotoxicity, cytokine release syndrome, B-cell aplasia, and graft versus host disease.

Tertiary outcomes

Tertiary outcomes that will be extracted include overall survival, patient experience, health-related quality of life, and health utility.

Overall survival

We will define overall survival as the time from the start of treatment to the time of death from any cause.

Patient experience

Patient experience combines a number of different dimensions including patient satisfaction, expectations, and outcomes that occur throughout the experience of clinical treatment [26].

Health-related quality of life

Health-related quality of life is a multidimensional concept that describes an individual's self-perceived health status [27].

Health utility

Health utility measures reflect the preference values that patients attach to their overall health status. A utility value is the global measure of health status; it summarizes the effects of an intervention into one value between 0 (equal to death) and 1 (equal to perfect health). Due to the variety of measures for patient experience, health-related quality of life, and health utility used in clinical trials, all reported indices will be considered.

Outcome follow-up periods

Early and durable response will be recorded among included studies. All time points will be considered due to the anticipated variability in follow-up. The median duration of follow-up will also be recorded for all studies.

Risk of bias assessment

Currently, no tool exists to assess the risk of bias for single arm interventional studies. To assess the risk of bias tool for single arm interventional studies, we have modified the Institute of Health Economics (IHE) risk of bias tool for case series studies [29] and incorporated items from the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [30]. This modified IHE tool includes assessment of the study objective, design, study population, intervention and co-interventions, outcome measures (i.e. blinding, incomplete outcome data such as participants lost to follow-up and selective outcome reporting), statistical analysis, results and conclusions, and conflicts of interest. Each item will be scored as high risk, moderate risk, or low risk of bias. For each item, a score of three will indicate a low risk of bias, two moderate risk of bias, and one highest risk of bias. A sum of items among each study will also be performed to provide the overall appraisal score for each individual study. The overall risk of bias results from

the quality assessment will be provided in a risk of bias graph using Review Manager 5.3 (London, UK). These judgments will be made independently by two review authors (FH, ML) based on the judging criteria provided for the modified IHE risk of bias tool for interventional study designs (see supplemental appendix 2). Disagreements will be resolved first by discussion and then by consulting a third author (DF) for arbitration.

Meta-bias assessment (or Risk of bias across studies)

A recent study demonstrated that traditional funnel plots may be a potentially misleading tool to assess publication bias in meta-analyses of proportion studies, particularly where low or high event rates exist [32]. The same study suggested an alternative funnel plot using study sample size on the vertical axis instead of log odds of the event rate may be a more accurate measure of publication bias [32]. Therefore, our review will follow these recommendations to assess publication bias and use an alternative funnel plot of sample size on the vertical axis and inverse of the standard error log odds in the horizontal axis.

Summary measures and synthesis of results

We will perform a meta-analysis to synthesize the prevalence of outcomes reported. For patients with hematologic malignancies, studies will be stratified by CD19 and non-CD19 targeted antigens. Dichotomous outcomes will be reported as proportions with 95% confidence intervals (CI). Continuous outcomes will be reported descriptively. A random effects model will be employed using the DerSimonian and Laird random effects method in order to pool outcome proportions (Comprehensive Meta-analysis 2.0, Englewood, USA). Continuity corrections will be implemented in order to account for 0 and 100% event rates (0.5 was added to all cells for trials with zero-events). Heterogeneity of effect sizes in the pooled proportions will be calculated

among included studies, for studies with n > 1, using the Cochrane I^2 statistic. The following thresholds are suggested to interpret the I^2 statistic: 0–40% (low heterogeneity), 30–60% (moderate heterogeneity), 50–90% (substantial heterogeneity), and 75–100% (considerable heterogeneity) [31]. If there is considerable heterogeneity, sources of heterogeneity will explored.

Subgroup Analyses

We will perform several *a priori* subgroup analyses to identify any subpopulations that may be associated with different CAR-T therapy effectiveness. These analyses will include stratification of studies based on the type of malignancy (i.e. non-Hodgkin's lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, metastatic breast cancer, etc.), pediatric versus adult populations, interleukin-2 administration to cell and/or patient, lymphodepletion, T cell origin (autologous versus allogeneic), T cell culture time, total cell dose, T cell persistence time, variability in T-cell culture time, dose and persistence time, fresh versus frozen CAR-T product administered, and C19 CAR-T cells versus all other construct types.

Reporting of Review

Our findings will be reported in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [33]. A completed copy of the checklist will be provided as a supplementary document to the main report.

Confidence in cumulative estimate

The quality of the treatment effects will be evaluated use the systematic and comprehensive approach known as Grading of Recommendations, Assessment, Development and Evaluations (GRADE). This approach is recognized as a highly effective method in terms of comparing the treatment effectiveness and quality to clinical recommendations. The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Quality will be assigned as one of four GRADE scores (0 to 4) reflecting high, moderate, low, or very low quality evidence (34). High quality evidence reflects a high degree of confidence in the estimate of effect whereas very low quality evidence indicates a high degree of uncertainty regarding the estimate of effect.

List of abbreviations

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BioCanRx, Biotherapeutics for Cancer Treatment; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; DistillerSR, Distiller systematic review; GRADE, grading of recommendations, assessment, development and evaluations; IHE, Institute of Health Economics; RECIST, response evaluation criteria in solid tumors.

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or publication of the study results. ML salary is supported by The Ottawa Hospital Anesthesia Alternate Funds Association.

COMPETING INTERESTS

The authors have no declarations of conflicts of interest.

ETHICS AND DISSEMINATION

Ethics considerations

Not applicable.

Dissemination

The results of the study will be submitted for publication to a peer-reviewed journal and presented at relevant national and international conferences and scientific meetings to promote knowledge transfer.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Amendments

If amendments are required for this protocol, date of each amendment will be provided with a description and rationale for the change in this section.

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Sponsor

BioCanRx funded this research.

Role of sponsor

BioCanRx is funding this systematic review; funding will support the collection of data, data management and analyses. BioCanRx will not be involved in any other aspect of the project, such as the design of the project's protocol and analysis plan, the collection of data and analyses. The funder will have no input on the interpretation or publication of the study results.

AUTHORS' CONTRIBUTIONS

CRediT taxonomy was used to describe author contributions (see supplemental appendix 3). ML is the guarantor. Conceptualization, ML, EG, and DF; Methodology, TR, RH, ML, NA, MS, HA, EG, DF and BH; Writing - Original draft, EG; Resources, RS and RH; Writing - Review and Editing, RS, RH, ML, NK, MS, KT, JP, HA, and DF; Supervision and Funding Acquisition, ML and DF; Project Administration, EG.

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Appendix 1. Representative Search Strategy

Hematologic malignancies:

Database: Embase Classic+Embase, EBM Reviews - Cochrane Central Register of Controlled Trials, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R).

Search Strategy:

1 ((chimeric antigen adj2 receptor*) and (therap* or treat* or immunity or immunotherap* or cell*)).tw.

2 ((car adj3 t adj5 therap*) or (car adj3 t adj5 treat*)).tw.

3 (car adj3 t adj3 immunotherap*).tw.

4 (car therap* or (car adj2 t adj2 cell*)).tw.

5 ((modified or engineered) adj2 (t cell* or t lymphocyte*)).tw.

6 chimeric antigen receptor/

7 or/1-6

8 (h?ematolog* cancer* or lymphoid malignanc* or b cell malignan* or h?ematolog* neoplasm* or h?ematolog* malignanc* or lymphoma* or leuk?emi* or myeloma* or nonhodgkin* or non hodgkin* or t cell malignan*).tw.

9 hematologic malignancy/ or exp lymphoma/ or exp leukemia/ or exp multiple myeloma/

Solid tumors:

Database: Embase Classic+Embase, EBM Reviews - Cochrane Central Register of Controlled Trials, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R).

Search Strategy:

1 ((chimeric antigen adj2 receptor*) and (therap* or treat* or immunity or immunotherap* or cell*)).tw.

2 ((car adj3 t adj5 therap*) or (car adj3 t adj5 treat*)).tw.

3 (car adj3 t adj3 immunotherap*).tw.

4 (car therap* or (car adj2 t adj2 cell*)).tw.

5 ((modified or engineered) adj2 (t cell* or t lymphocyte*)).tw.

6 chimeric antigen receptor/

7 or/1-6

8 exp solid tumor/

9 (solid adj (tumo?r* or malignan* or cancer)).tw.

10 exp breast cancer/

11 exp colon cancer/

12 exp rectum cancer/

13 colorectal cancer/

14 exp kidney cancer/

15 exp lung cancer/

16 exp prostate cancer/

17 exp pancreas cancer/

18 exp bladder cancer/

19 ((breast or lung or rect* or colorect* or colon or prostat* or renal or kidney or bladder or pancrea*) adj2 (cancer* or neoplasm* or carcinoma* or tumo?r*)).tw.

20 exp skin cancer/ or cutaneous melanoma/

21 (Skin adj2 (cancer or neoplasm*)).tw.

22 melanoma.tw.

23 brain cancer/

24 (brain adj2 (cancer or neoplasm* or tum?or*)).tw.

25 (glioma* or glioblastoma*).tw.

26 exp sarcoma/

27 sarcoma.tw.

28 malignant mesothelioma/

29 mesothelioma.tw.

30 liver cancer/

31 ((liver or hepatic or Hepatocellular) adj2 (cancer* or neoplasm* or carcinoma* or tumo?r*)).tw.

Appendix 2. Modified Institute of Health Economics Tool

Question Text	Answer Text
Was the hypothesis/ aim/ objective of the study stated? Yes = The hypothesis/aim/objective was reported (includes patients, intervention and outcome). Partial/ unclear = Only one or two components (patients, intervention, or outcome) were included. No = The hypothesis/aim/ objective was not reported.	Yes
	Partial/ unclear
	No
Was the study conducted prospectively? Yes = It was clearly stated that the study was conducted prospectively. Partial/ unclear = Unclear or no information was provided. No = The study clearly stated it was a retrospective study.	Yes
	Partial/ unclear
	No
Were patients from more than one centre? For example, you can deduce single centre if they state "Data was taken from the Sloan Memorial Research Centre". Yes = Patients were from more than one centre (multicentre study). Partial/ unclear = Unclear where the patients came from. No = Patients were from one centre.	Yes
	Partial/ unclear
	No
Were patients recruited consecutively? Note: Not based on previously published protocols. Must be stated in this paper. Yes = There was a clear statement or it was clear from the context that the patients were recruited consecutively; or the study stated that all eligible patients were recruited. Partial/ unclear = No information was provided about the method used to recruit patients in the study. No = The study clearly stated that patients were not recruited consecutively; or the patients were recruited based on other criteria such as access to intervention. N/A = N of 1 study.	Yes
	Partial/ unclear
	No
	N/A
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated? Note: Not based on previously published protocols. Must be stated in this paper. Yes = Both inclusion and exclusion criteria were reported.	Yes

Partial/ unclear = Either inclusion OR exclusion were reported. No = Neither inclusion nor exclusion criteria were reported.	
	Partial/unclear
	No
Were the characteristics of the patients included in the study described? Relevant characteristics: age, sex, malignancy type, lymphodepletion, previous treatment, concomitant treatments, co-morbidities. Yes = All of the relevant patient characteristics were reported. Partial/ unclear = >= 1 of the relevant characteristics were reported. No = None of the relevant characteristic were reported.	Yes
	Partial/ unclear
	No
Did patients enter the study at a similar point in the disease? Yes = The paper states that entering patients are in relapsed/ refractory setting. Partial/ unclear = There was no baseline information on patients' characteristics to make a judgment. No = There was a wide range in the severity of the disease and co-morbidities of patients at baseline. N/A = N of 1 study.	Yes
	Partial/ unclear
	No
	N/A
Was the intervention of interest described? Relevant characteristics: T-cell origin, CD configuration (type (i.e. CD19), co-stimulatory domain(s), dosage regimen (dose, frequency, duration). Yes = All of the relevant characteristics of the intervention were reported. Partial/unclear = Some of the relevant characteristics of the intervention were reported. No = None of the relevant characteristics of the intervention were reported.	Yes
	Partial/unclear
	No
Were additional interventions clearly described? i.e. chemotherapy, HSCT, radiation. Yes = All of the most relevant characteristics (type, dose, frequency administration, duration) of the co-intervention were reported Partial/ unclear = Some but not all of the most relevant characteristics of the co-intervention were reported. No = No information about the co-intervention was provided; or only the name of the co-intervention was mentioned.	Yes
	Partial/ unclear

	No
Were relevant outcome measures established a priori in the introduction or methods section? Yes = All relevant outcome measures were stated. Partial/ unclear = Some, but not all of the relevant outcome measures were stated. No = None of the relevant outcome measures were stated.	Yes
	Partial/ unclear
	No
Were outcome assessors blinded to the intervention that patients received? i.e. Did the study have 'independent outcome assessors'? Yes = The outcomes were assessed by individuals who were not aware of patient intervention. - SELECT where blinding is not necessary. i.e. Mortality is the outcome. - SELECT where the blinding to the outcome does not influence the assessment. i.e. Response to CAR-T. Partial/ unclear = The study did not report whether the outcome assessors were aware of the intervention. No = It was clearly stated or obvious from the context that individuals assessing outcomes were unblinded.	Yes
	Partial/ unclear
	No
Were the relevant outcomes measured using appropriate objective or subjective methods? Yes = Complete response/remission and >=1 secondary outcomes (i.e, overall response rate, non-relapse mortality, relapse, overall survival, adverse events (infection, neurotoxicity, cytokine release syndrome, B-cell aplasia, graft versus host disease, other types will be grouped by organ system affected and severity) Partial/ unclear = >=1 secondary outcomes (listed in OUR protocol) were reported No = None of the outcomes listed in OUR protocol were reported.	Yes
	Partial/ unclear
	No
Were the relevant outcome measures made before and after the intervention? Yes = The relevant outcome measures were made pre- and post-intervention; or the baseline measurements were not possible (ex. death). Partial/ unclear = The study did not report when the outcome measures were made. No = The outcome measures were only made post-intervention.	Yes
	Partial/ unclear

	No
The study does not perform selective outcome reporting. Yes = The study protocol is registered and all of the study's pre-specified outcomes of interest were stated in the methods section. Partial/ unclear = Either study protocol registered or the study's pre-specified outcomes of interest were stated in the methods section. No = No study protocol registered and none of the study's pre-specified outcomes of interest were stated in the methods section.	Yes
	Partial/unclear
	No
Were details of the statistical tests reported? Yes = The statistical tests were reported in the study. Partial/unclear = Statistical tests only partially described or reported elsewhere (e.g previous paper, or protocol). No = The statistical tests were not described in the study. N/A = N of 1 study.	Yes
	Partial/unclear
	No
	N/A
Was follow-up period reported? Yes = follow-up information was reported. No = Length of follow-up was not reported.	Yes
	No
Did the study provide estimates of random variability in the data analysisof relevant outcomes? Yes = Estimates of the random variability (ex. SE, SD, CI) were reported for all relevant outcomes and/or could be calculated from the raw data. Partial/ unclear = Estimates if the random variability were reported for some, but not all relevant outcomes. No = Estimates of the random variability were not reported for any of the relevant outcomes. N/A = N of 1 study.	Yes
	Partial/unclear
	No
	N/A
Were the adverse events reported? Includes: Infection, neurotoxicity, cytokine release syndrome, B-cell aplasia, and graft versus host disease. Yes = All adverse events were reported. Partial/ unclear = Unclear if all the adverse events were reported. No = No information about adverse events reported.	Yes
	Partial/ unclear
	No

Were both competing interests and sources of support for the study reported? Yes = Both competing interests and sources of support (financial or other) received for the study were reported; or the absence of support was acknowledged. Partial/ unclear = Either the competing interest or source of support was reported. No = Neither competing interests nor sources of support were reported.	Yes
	Partial/ unclear
	No

Appendix 3. Contributor roles taxonomy

Contributor Role[1]	Role Definition
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims.
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse.
Formal Analysis	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.
Funding Acquisition	Acquisition of the financial support for the project leading to this publication.
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.
Methodology	Development or design of methodology; creation of models
Project Administration	Management and coordination responsibility for the research activity planning and execution.
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs.
Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation.
Writing – Original Draft Preparation	Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation).
Writing – Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.

[1]Author contributions based on contributor role taxonomy defined previously by Brand *et al.* (50)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	4
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	20
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	19
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	19
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	19
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	19
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	5-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	7
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	7-8
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	9
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	10
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	10
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	10
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	10-11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	11-15
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	15-16
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	16-17
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of	☒	☐	16-17

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		consistency (e.g., I^2, Kendall's tau)			
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	17
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	16-17
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	18

BMJ Open

Efficacy and safety of Chimeric Antigen Receptor T-cell (CAR-T) therapy in patients with hematologic and solid malignancies: protocol for a systematic review and meta-analysis

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2017-019321.R1
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Date Submitted by the Author:	11-Oct-2017
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Primary Subject Heading:	Oncology
Secondary Subject Heading:	Haematology (incl blood transfusion), Pharmacology and therapeutics

Keywords:	Leukaemia < HAEMATOLOGY, Lymphoma < HAEMATOLOGY, Myeloma < HAEMATOLOGY, Chimeric Antigen Receptor, CAR-T, Malignancy

Efficacy and safety of Chimeric Antigen Receptor T-cell (CAR-T) therapy in patients with hematologic and solid malignancies: protocol for a systematic review and meta-analysis

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ABSTRACT

Introduction: Patients with relapsed or refractory malignancies have a poor prognosis. Immunotherapy with Chimeric Antigen Receptor T (CAR-T) cells redirects a patient's immune cells against the tumor antigen. CAR-T cell therapy has demonstrated promise in treating patients with several hematologic malignancies, including acute B cell lymphoblastic leukemia and B cell lymphomas. CAR-T cell therapy for patients with other solid tumors is also being tested. Safety is an important consideration in CAR-T cell therapy given the potential for serious adverse events, including death. Previous reviews on CAR-T cell therapy have been limited in scope and methodology. Herein we present a protocol for a systematic review to identify CAR-T cell interventional studies and examine the safety and efficacy of this therapy in patients with hematology malignancies and solid tumors.

Methods and analysis: We will search MEDLINE, including In-Process and Epub Ahead of Print, EMBASE, and the Cochrane Central Register of Controlled Trials from 1946 to 22 February 2017. Studies will be screened by title, abstract, and full text independently and in duplicate. Studies that report administering CAR-T of any chimeric antigen receptor construct targeting antigens in patients with hematologic malignancies and solid tumors will be eligible for inclusion. Outcomes to be extracted will include complete response rate (primary outcome), overall response rate, overall survival, relapse, and adverse events. A meta-analysis will be performed to synthesize the prevalence of outcomes reported as proportions with 95% confidence intervals. The potential for bias within included studies will be assessed using a modified Institute of Health Economics tool. Heterogeneity of effect sizes will be determined using the Cochrane I^2 statistic.

Ethics and Dissemination: The review findings will be submitted for peer-reviewed journal publication and presented at relevant conferences and scientific meetings to promote knowledge transfer.

Registration: The protocol has been registered with the International Prospective Register of Systematic Reviews (CRD42017075331).

Word count (abstract): 298

STRENGTHS AND LIMITATIONS OF THIS STUDY

1. A major methodological limitation is that all eligible studies are expected to be single arm and have no comparator group. This may increase risk of bias when interpreting results.
2. We provide a comprehensive plan to address limitations of meta-analysis of single arm studies that includes use a modified Institute of Health Economics tool for assessing risk of bias in single arm interventional studies. Our approach can serve as a model for future systematic reviews assessing early-phase clinical data that is often single arm with no control comparison.

INTRODUCTION

Among patients with relapsed and refractory malignancies, chimeric antigen receptor T (CAR-T) cell therapy is a novel immunotherapy that has shown promise in both pre-clinical and early clinical studies. This therapy allows for CARs directed against tumour associated antigens (e.g. CD19, HER-2) to be introduced into a patient's T cells; this serves to reprogram these cells to target the patient's tumor cells. A number of small clinical trials using anti-CD19 CAR-T cells in hematologic malignancies have demonstrated sustained responses in patients with advanced disease [1-5]. CAR-T cell therapy for solid malignancies has also identified a number of

potential cancer-specific targets and previous pre-clinical studies investigating efficacy and feasibility show promise [6].

In spite of some evidence of efficacy of CAR-T cell therapy against some malignancies, there are a number of safety concerns that have been identified. Trials conducted by Juno Therapeutics and Kite Pharma reported mortality among patients with hematologic malignancy treated with CAR-T cell therapy [7, 8]. The Juno Therapeutics trial was closed after the death of five patients from cerebral edema linked to CAR-T cell therapy [9]. Previous trials investigating CAR-T cell therapy among patients with solid tumors have reported adverse events from treatment including anaphylaxis and cardiac arrest [10]. Past studies have also reported other challenges in applying CAR-T cell therapy to solid tumors, including a scarcity of tumor associated antigen targets, the potent immunosuppressive effects of the tumor microenvironment, and the limited trafficking of CAR-T cells to tumor sites [11, 12].

Due to the variability and small size of clinical trials investigating CAR-T therapy there is a need for a systematic review to evaluate its efficacy and safety. Although no systematic review currently exists for CAR-T therapy among solid tumors, we have identified four publications that self-identified as systematic reviews studying the efficacy and safety of CAR-T therapy for patients with hematologic malignancies [13, 14-16]. However, there were significant limitations in the scope and/or methodologies in these earlier reviews. Zhu *et al.* only considered CD19 targeted CAR-T therapies, did not report differences between adult and pediatric populations, and employed a non-systematic search strategy [14]. Anwer *et al.* only included allogeneic T-cells, whereas most CAR-T cell therapy uses autologous cells [15]. Another systematic review

by Zhang *et al.* only considered CD19 CAR-T therapies and was published in journal controlled by a predatory publisher [13, 17]. Finally, while titled as a systematic review, Holzinger *et al.* is only a narrative review [16]. Given these limitations of previous publications, along with rapid evolution of the CAR-T field, there is a need for a current systematic review, as we present here, that adheres to rigorous, state-of-the-art methods and summarizes the findings among both solid tumors and hematologic malignancies.

Our systematic review will clarify the determinants of efficacy and safety of CAR-T therapy and identify gaps in current practice and knowledge. This will also be the first review to investigate CAR-T therapy among patients with solid tumors. We expect the results from this clinical systematic review will help inform the design of clinical trials. We also summarize our approach to appraise and analyze single arm interventional studies that are typically conducted for early phase biotherapeutic trials; we believe this approach may be replicated for other systematic reviews of early phase clinical data.

Protocol

Our review protocol is reported in accordance with the Preferred Reporting Items in Systematic reviews and Meta-Analysis-Protocol guidelines (see supplemental research checklist) [18].

Research objectives

We will review controlled and uncontrolled interventional studies of CAR-T cell therapy to examine the safety and efficacy of this treatment in patients with relapsed or refractory hematological malignancies and solid tumors.

METHODS AND ANALYSIS

Eligibility criteria

Studies will be selected according to the eligibility criteria detailed in Table 1. Interventional studies with and without comparators will be included. We anticipate that many of the included studies will be single-arm interventional studies. Full text articles in any language will be considered. Unpublished gray literature, abstracts, commentaries, letters, reviews, and editorials will be excluded [19].

Table 1. Population, Intervention, Comparison, Outcome, and Study design breakdown of study eligibility criteria

Category	Description of criteria
Population	Patients with solid tumor or hematologic malignancies
Intervention	Chimeric antigen receptor T cell therapy
Comparator(s)	Studies with or without any comparator will be considered
Outcome(s)	Primary outcome: • Complete response Secondary outcomes: • Overall response (hematological) or objective response (solid) • Progressive disease • Relapse • Overall survival • Adverse events (infection, neurotoxicity, cytokine release syndrome, B-cell aplasia, graft versus host disease, other types will be grouped by organ system affected and severity) Tertiary outcomes: • Health-related quality of life • Health utility measures • Patient experience
Study design	Interventional: +/- controlled, +/- randomized

Information sources

We will search MEDLINE (OVID interface, including In-Process and Epub Ahead of Print), EMBASE (OVID interface), and the Cochrane Central Register of Controlled Trials (Wiley interface) from 1946 to 22 February 2017 and plan to update our search prior to submission for publication. Clinical trial registries will be searched to identify ongoing and completed trials. Specifically, ClinicalTrials.gov and the International Prospective Register of Systematic Reviews will be searched to identify ongoing or recently completed trials or systematic reviews. In order to further ensure a comprehensive literature search, we will examine reference lists of included studies or relevant reviews identified through the search. Authors of the studies included in the present review will be contacted for review of reported outcomes. Finally, we will circulate a bibliography of included articles to the systematic review team for feedback.

Search strategy

Specific search strategies will be created in collaboration with a Health Sciences Librarian (RS) with expertise in the design of systematic searches. The literature search strategies will be developed using key words related to CAR-T cell therapy as well as hematological malignancies and solid tumors. Search strategies will use controlled vocabulary (e.g. Receptors, Antigen, T-Cell) and keywords (e.g. CAR-T). The syntax and subject headings used in the finalized EMBASE strategy will be adapted to the other databases. A validated search filter for clinical studies will be applied. Both qualitative and quantitative studies will be sought. No study design, date or language limits will be imposed on the search. A Peer Review of Electronic Search Strategy will be performed by a second librarian who is not associated with the project [20]. A

draft of the Medline (OVID interface) search strategy for hematologic and solid tumors is shown in supplemental appendix 1.

Study records

The literature search results will be uploaded to Distiller Systematic Review Software (DistillerSR®, Evidence Partners, Ottawa). DistillerSR is a cloud-based software program that provides transparent, reproducible, and audit-ready results necessary for accurate review.

Data collection process

Two review authors (EG, ML) will independently screen the titles and abstracts from the search results using the pre-defined inclusion criteria presented in Table 1. A calibration test will be performed to refine the screening question prior to formally commencing the screening process. For all titles that appear to meet the inclusion criteria or where there is any uncertainty, we will access the full text. Two review authors (EG, FH) will assess the eligibility of full reports. Disagreement will be resolved through discussion with a third party member (DF, HA, ML, NK). We will record the reasons for excluding studies. In the case of screening eligibility of non-English full-text articles, Ottawa Hospital Employees with fluency in the article languages will first be contacted for assistance determining article eligibility. If the article meets the eligibility criteria for inclusion in the review, a verbatim translation using the scientific translation services at the Ottawa Hospital will be used.

Data items

Standardized drafts of data extraction forms were designed to extract all information of interest from the screened studies in adherence with the Effective Practice and Organisation of Care guidelines [21]. The drafts will be used to inform the construction of the online data abstraction program (DistillerSR). Data will be extracted independently and in duplicate from each eligible study (EG, FH). A calibration exercise will be conducted prior to formally starting data abstraction. Demographic information, methodology, intervention details, and outcomes will be recorded. Reviewers will resolve disagreements by discussion or by conferring with one of two arbitrators (ML, DF), who will adjudicate to resolve disagreements. Where uncertainty is identified, we will contact study authors for more information.

Study characteristics to be extracted will include the journal title, the first author, the inclusion criteria (outlined in Table 1), patient characteristics (mean age, sex, malignancy diagnosis), trial design, type and source of financial support, publication status from trial reports, and study sample size. Study intervention characteristics to be extracted will include lymphodepletion method (preconditioning agents), previous treatment (ablative, non-ablative), failed transplant, co-morbidities, concomitant medications, and length of follow-up. CAR-T intervention characteristics to be extracted will detail manufacturing and cell product characteristics, including: fresh or frozen, T-cell origin, selection of T cell subsets, T cell expansion method including cell culture duration, CAR target antigen, CAR antigen, CAR molecular structure (i.e. affinity domain, hinge domain, transmembrane domain, co-stimulatory domain(s), signaling domain), transfection/transduction method, and the therapeutic regimen (CAR-T dose, frequency, duration, route of administration). Absolute lymphocyte counts prior to CAR-T cell therapy administration will also be recorded as this has useful information for patient eligibility

of CAR-T cells. Among solid tumors, the tumour regression grade will be reported when available. When necessary, we will obtain measures of central tendency and dispersion of data by analyzing the figures and tables or by contacting the authors. Whenever possible, the results from an intention to treat analysis will be used.

Outcome justification and prioritization

Primary outcome

Complete response, our primary outcome, will be defined by type of disease: hematological malignancies acute lymphocytic leukemia (ALL) or acute myeloid leukemia (AML) and solid tumors. If complete response is not feasible, secondary response outcomes will be reported using best overall response when available. Best overall response will be defined according to the response evaluation criteria in solid tumors (RECIST) guidelines where patients will be assigned into one of the following categories: Complete response, partial response, stable disease, progression, or inevaluable for response [22]. Studies that recruit patients in complete remission at the initiation of CAR-T cell therapy will not be included in the complete response data reported.

ALL and AML

For patients with ALL or AML, in studies that: 1) do not provide a definition for complete response, it will be considered hematologic response; 2) report minimal residual disease,

response will be defined by any response criteria, including molecular, morphological, and immunological. The sensitivity of the assay used will also be extracted for molecular response.

Solid tumors

For patients with solid tumors, target and non-target lesions recorded at measurement baseline will be defined according to the RECIST guidelines. Target lesions may include up to five lesions which will likely include lesions with the longest diameters. Non-target lesions will be inclusive of all other lesions (or disease targets), including pathological lymph nodes. Target lesion and non-target lesion complete responses will be defined as disappearance of all target lesions and non-target lesions, respectively, where non-target lesions must be accompanied by normalization of tumor marker level as defined by RECIST guidelines [22]. In patients with solid tumors, any pathological lymph nodes (among target or non-target lesions) must decrease in the short axis to less than 10mm [22]. Furthermore, in studies that report tumor regression grading of zero, response will be defined as pathological response.

Secondary outcomes

Overall response, progression of disease, relapse, and adverse events are our secondary response outcomes to be measured.

Overall response or objective response

Overall response and objective response will be defined as the sum of partial or complete responses in both hematologic malignancies and solid tumors, respectively. In hematologic malignancies, partial response is considered when there has been a response to therapy but does not meet the criteria for complete response. In target lesion evaluation for solid tumors, partial response is defined as a 30% decrease in the sum of target lesion diameters (compared to baseline measures) [22].

Progressive disease

Progressive disease in hematologic malignancies is considered when evidence of disease increases in the peripheral blood or bone marrow, or progression or new extramedullary disease is identified. In solid tumors, progressive disease is defined as a relative increase in the sum of target lesions by 20% (smallest sum as reference), an absolute increase in target lesions by 5 mm, as well as appearance of any new lesions [22]. In both hematologic and solid tumors, stable disease is defined as not meeting criteria for partial response, complete response or progression.

Relapse

Relapse is defined as a patient who has a partial or complete response but then develops disease progression. Studies that recruit patients in complete remission at the initiation of CAR-T cell therapy will be descriptively reported in the proportion of the patients that relapse. For patients with lymphoma or chronic lymphocytic leukemia (CLL), response criteria are defined as per the RECIST guidelines [22]. Lastly, if CLL is identified as circulating disease in the peripheral blood and/or bone marrow only, the response criteria that is used for AML and ALL will be employed.

Adverse events

Adverse events secondary outcomes will be used to evaluate clinical safety of CAR-T cell therapy. Adverse events are a measure of unplanned or undesired symptoms or diagnoses that occur during the study, which were absent at baseline, or worsen over the course of the study [25]. In the setting of CAR-T cells, adverse events of special interest include infection, neurotoxicity, cytokine release syndrome, B-cell aplasia, and graft versus host disease.

Tertiary outcomes

Tertiary outcomes that will be extracted include overall survival, patient experience, health-related quality of life, and health utility.

Overall survival

We will define overall survival as the time from the start of treatment to the time of death from any cause.

Patient experience

Patient experience combines a number of different dimensions including patient satisfaction, expectations, and outcomes that occur throughout the experience of clinical treatment [26].

Health-related quality of life

Health-related quality of life is a multidimensional concept that describes an individual's self-perceived health status [27].

Health utility

Health utility measures reflect the preference values that patients attach to their overall health status. A utility value is the global measure of health status; it summarizes the effects of an intervention into one value between 0 (equal to death) and 1 (equal to perfect health). Due to the variety of measures for patient experience, health-related quality of life, and health utility used in clinical trials, all reported indices will be considered.

Outcome follow-up periods

Early and durable response will be recorded among included studies. All time points will be considered due to the anticipated variability in follow-up. The median duration of follow-up will also be recorded for all studies.

Risk of bias assessment

Currently, no tool exists to assess the risk of bias for single arm interventional studies. To assess the risk of bias tool for single arm interventional studies, we have modified the Institute of Health Economics (IHE) risk of bias tool for case series studies [29] and incorporated items from the Cochrane Collaboration's tool for assessing risk of bias in randomized trials [30]. This modified IHE tool includes assessment of the study objective, design, study population, intervention and co-interventions, outcome measures (i.e. blinding, incomplete outcome data such as participants lost to follow-up and selective outcome reporting), statistical analysis, results and conclusions, and conflicts of interest. Each item will be scored as high risk, moderate risk, or low risk of bias. For each item, a score of three will indicate a low risk of bias, two moderate risk of bias, and one highest risk of bias. A sum of items among each study will also be performed to provide the overall appraisal score for each individual study. The overall risk of bias results from the quality assessment will be provided in a risk of bias graph using Review Manager 5.3 (London, UK). These judgments will be made independently by two review authors (FH, ML) based on the judging criteria provided for the modified IHE risk of bias tool for interventional study designs (see supplemental appendix 2). Disagreements will be resolved first by discussion and then by consulting a third author (DF) for arbitration.

Meta-bias assessment (or Risk of bias across studies)

A recent study demonstrated that traditional funnel plots may be a potentially misleading tool to assess publication bias in meta-analyses of proportion studies, particularly where low or high event rates exist [32]. The same study suggested an alternative funnel plot using study sample size on the vertical axis instead of log odds of the event rate may be a more accurate measure of publication bias [32]. Therefore, our review will follow these recommendations to assess

publication bias and use an alternative funnel plot of sample size on the vertical axis and inverse of the standard error log point estimate in the horizontal axis.

Summary measures and synthesis of results

We will perform a meta-analysis to synthesize the prevalence of outcomes reported. For patients with hematologic malignancies, studies will be stratified by CD19 and non-CD19 targeted antigens. Dichotomous outcomes will be reported as proportions with 95% confidence intervals (CI). Continuous outcomes will be reported descriptively. A random effects model will be employed using the DerSimonian and Laird random effects method in order to pool outcome proportions (Comprehensive Meta-analysis 2.0, Englewood, USA). Continuity corrections will be implemented in order to account for 0 and 100% event rates (0.5 was added to all cells for trials with zero-events). Heterogeneity of effect sizes in the pooled proportions will be calculated among included studies, for studies with n > 1, using the Cochrane I^2 statistic. The following thresholds are suggested to interpret the I^2 statistic: 0–40% (low heterogeneity), 30–60% (moderate heterogeneity), 50–90% (substantial heterogeneity), and 75–100% (considerable heterogeneity) [31]. If there is considerable heterogeneity, sources of heterogeneity will be explored.

Subgroup Analyses

We will perform several *a priori* subgroup analyses to identify any subpopulations that may be associated with different CAR-T therapy effectiveness. These analyses will include stratification of studies based on the type of malignancy (i.e. non-Hodgkin's lymphoma, chronic lymphocytic leukemia, acute lymphocytic leukemia, metastatic breast cancer, etc.), pediatric versus adult

populations, interleukin-2 administration to cell and/or patient, lymphodepletion, T cell origin (autologous versus allogeneic), T cell culture time, total cell dose, T cell persistence time, variability in T-cell culture time, dose and persistence time, fresh versus frozen CAR-T product administered, and C19 CAR-T cells versus all other construct types.

Reporting of Review

Our findings will be reported in agreement with the Preferred Reporting Items for Systematic Reviews and Meta-analyses statement [33]. A completed copy of the checklist will be provided as a supplementary document to the main report.

Confidence in cumulative estimate

The quality of the treatment effects will be evaluated use the systematic and comprehensive approach known as Grading of Recommendations, Assessment, Development and Evaluations (GRADE). This approach is recognized as a highly effective method in terms of comparing the treatment effectiveness and quality to clinical recommendations. The quality of evidence will be assessed across the domains of risk of bias, consistency, directness, precision and publication bias. Quality will be assigned as one of four GRADE scores (0 to 4) reflecting high, moderate, low, or very low quality evidence (34). High quality evidence reflects a high degree of confidence in the estimate of effect whereas very low quality evidence indicates a high degree of uncertainty regarding the estimate of effect.

List of abbreviations

ALL, acute lymphocytic leukemia; AML, acute myeloid leukemia; BioCanRx, Biotherapeutics for Cancer Treatment; CAR-T, chimeric antigen receptor T cell; CD, cluster of differentiation; CLL, chronic lymphocytic leukemia; DistillerSR, Distiller systematic review; GRADE, grading of recommendations, assessment, development and evaluations; IHE, Institute of Health Economics; RECIST, response evaluation criteria in solid tumors.

FUNDING

This study is supported by a grant (Grant reference number: FY17 / CSEI4) from Biotherapeutics for Cancer Treatment (BioCanRx) a Canadian Network of Centres of Excellence. Funding will support the collection of data, data management and analyses. BioCanRx will not be involved in the design of the project's protocol, analysis plan, collection of data, analyses, or interpretation or publication of the study results. ML salary is supported by The Ottawa Hospital Anesthesia Alternate Funds Association.

COMPETING INTERESTS

The authors have no declarations of conflicts of interest.

ETHICS AND DISSEMINATION

Ethics considerations

Not applicable.

Dissemination

The results of the study will be submitted for publication to a peer-reviewed journal and presented at relevant national and international conferences and scientific meetings to promote knowledge transfer.

Consent for publication

Not applicable.

Availability of data and material

Not applicable.

Amendments

If amendments are required for this protocol, date of each amendment will be provided with a description and rationale for the change in this section.

Sources

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Sponsor

BioCanRx funded this research.

Role of sponsor

BioCanRx is funding this systematic review; funding will support the collection of data, data management and analyses. BioCanRx will not be involved in any other aspect of the project, such as the design of the project's protocol and analysis plan, the collection of data and analyses. The funder will have no input on the interpretation or publication of the study results.

AUTHORS' CONTRIBUTIONS

CRediT taxonomy was used to describe author contributions (see supplemental appendix 3). ML is the guarantor. Conceptualization, ML, EG, and DF; Methodology, TR, RH, ML, NK, MS, HA, EG, DF and BH; Writing - Original draft, EG; Resources, RS and RH; Writing - Review and Editing, RS, RH, ML, MD, NK, MS, KT, JP, HA, FH, DJ, and DF; Supervision and Funding Acquisition, ML and DF; Project Administration, EG.

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Appendix 1. Representative Search Strategy

Hematologic malignancies:

Database: Embase Classic+Embase, EBM Reviews - Cochrane Central Register of Controlled Trials, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R).

Search Strategy:

1 ((chimeric antigen adj2 receptor*) and (therap* or treat* or immunity or immunotherap* or cell*)).tw.

2 ((car adj3 t adj5 therap*) or (car adj3 t adj5 treat*)).tw.

3 (car adj3 t adj3 immunotherap*).tw.

4 (car therap* or (car adj2 t adj2 cell*)).tw.

5 ((modified or engineered) adj2 (t cell* or t lymphocyte*)).tw.

6 chimeric antigen receptor/

7 or/1-6

8 (h?ematolog* cancer* or lymphoid malignanc* or b cell malignan* or h?ematolog* neoplasm* or h?ematolog* malignanc* or lymphoma* or leuk?emi* or myeloma* or nonhodgkin* or non hodgkin* or t cell malignan*).tw.

9 hematologic malignancy/ or exp lymphoma/ or exp leukemia/ or exp multiple myeloma/

Solid tumors:

Database: Embase Classic+Embase, EBM Reviews - Cochrane Central Register of Controlled Trials, Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R).

Search Strategy:

1 ((chimeric antigen adj2 receptor*) and (therap* or treat* or immunity or immunotherap* or cell*)).tw.

2 ((car adj3 t adj5 therap*) or (car adj3 t adj5 treat*)).tw.

3 (car adj3 t adj3 immunotherap*).tw.

4 (car therap* or (car adj2 t adj2 cell*)).tw.

5 ((modified or engineered) adj2 (t cell* or t lymphocyte*)).tw.

6 chimeric antigen receptor/

7 or/1-6

8 exp solid tumor/

9 (solid adj (tumo?r* or malignan* or cancer)).tw.

10 exp breast cancer/

11 exp colon cancer/

12 exp rectum cancer/

13 colorectal cancer/

14 exp kidney cancer/

15 exp lung cancer/

16 exp prostate cancer/

17 exp pancreas cancer/

18 exp bladder cancer/

19 ((breast or lung or rect* or colorect* or colon or prostat* or renal or kidney or bladder or pancrea*) adj2 (cancer* or neoplasm* or carcinoma* or tumo?r*)).tw.

20 exp skin cancer/ or cutaneous melanoma/

21 (Skin adj2 (cancer or neoplasm*)).tw.

22 melanoma.tw.

23 brain cancer/

24 (brain adj2 (cancer or neoplasm* or tum?or*)).tw.

25 (glioma* or glioblastoma*).tw.

26 exp sarcoma/

27 sarcoma.tw.

28 malignant mesothelioma/

29 mesothelioma.tw.

30 liver cancer/

31 ((liver or hepatic or Hepatocellular) adj2 (cancer* or neoplasm* or carcinoma* or tumo?r*)).tw.

Appendix 2. Modified Institute of Health Economics Tool

Question Text	Answer Text
Was the hypothesis/ aim/ objective of the study stated? Yes = The hypothesis/aim/objective was reported (includes patients, intervention and outcome). Partial/ unclear = Only one or two components (patients, intervention, or outcome) were included. No = The hypothesis/aim/ objective was not reported.	Yes
	Partial/ unclear
	No
Was the study conducted prospectively? Yes = It was clearly stated that the study was conducted prospectively. Partial/ unclear = Unclear or no information was provided. No = The study clearly stated it was a retrospective study.	Yes
	Partial/ unclear
	No
Were patients from more than one centre? For example, you can deduce single centre if they state "Data was taken from the Sloan Memorial Research Centre". Yes = Patients were from more than one centre (multicentre study). Partial/ unclear = Unclear where the patients came from. No = Patients were from one centre.	Yes
	Partial/ unclear
	No
Were patients recruited consecutively? Note: Not based on previously published protocols. Must be stated in this paper. Yes = There was a clear statement or it was clear from the context that the patients were recruited consecutively; or the study stated that all eligible patients were recruited. Partial/ unclear = No information was provided about the method used to recruit patients in the study. No = The study clearly stated that patients were not recruited consecutively; or the patients were recruited based on other criteria such as access to intervention. N/A = N of 1 study.	Yes
	Partial/ unclear
	No
	N/A
Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated? Note: Not based on previously published protocols. Must be stated in this paper. Yes = Both inclusion and exclusion criteria were reported.	Yes

Partial/ unclear = Either inclusion OR exclusion were reported. No = Neither inclusion nor exclusion criteria were reported.	
	Partial/unclear
	No
Were the characteristics of the patients included in the study described? Relevant characteristics: age, sex, malignancy type, lymphodepletion, previous treatment, concomitant treatments, co-morbidities. Yes = All of the relevant patient characteristics were reported. Partial/ unclear = >= 1 of the relevant characteristics were reported. No = None of the relevant characteristic were reported.	Yes
	Partial/ unclear
	No
Did patients enter the study at a similar point in the disease? Yes = The paper states that entering patients are in relapsed/ refractory setting. Partial/ unclear = There was no baseline information on patients' characteristics to make a judgment. No = There was a wide range in the severity of the disease and co-morbidities of patients at baseline. N/A = N of 1 study.	Yes
	Partial/ unclear
	No
	N/A
Was the intervention of interest described? Relevant characteristics: T-cell origin, CD configuration (type (i.e. CD19), co-stimulatory domain(s), dosage regimen (dose, frequency, duration). Yes = All of the relevant characteristics of the intervention were reported. Partial/unclear = Some of the relevant characteristics of the intervention were reported. No = None of the relevant characteristics of the intervention were reported.	Yes
	Partial/unclear
	No
Were additional interventions clearly described? i.e. chemotherapy, HSCT, radiation. Yes = All of the most relevant characteristics (type, dose, frequency administration, duration) of the co-intervention were reported Partial/ unclear = Some but not all of the most relevant characteristics of the co-intervention were reported. No = No information about the co-intervention was provided; or only the name of the co-intervention was mentioned.	Yes
	Partial/ unclear

	No
Were relevant outcome measures established a priori in the introduction or methods section? Yes = All relevant outcome measures were stated. Partial/ unclear = Some, but not all of the relevant outcome measures were stated. No = None of the relevant outcome measures were stated.	Yes
	Partial/ unclear
	No
Were outcome assessors blinded to the intervention that patients received? i.e. Did the study have 'independent outcome assessors'? Yes = The outcomes were assessed by individuals who were not aware of patient intervention. - SELECT where blinding is not necessary. i.e. Mortality is the outcome. - SELECT where the blinding to the outcome does not influence the assessment. i.e. Response to CAR-T. Partial/ unclear = The study did not report whether the outcome assessors were aware of the intervention. No = It was clearly stated or obvious from the context that individuals assessing outcomes were unblinded.	Yes
	Partial/ unclear
	No
Were the relevant outcomes measured using appropriate objective or subjective methods? Yes = Complete response/remission and >=1 secondary outcomes (i.e, overall response rate, non-relapse mortality, relapse, overall survival, adverse events (infection, neurotoxicity, cytokine release syndrome, B-cell aplasia, graft versus host disease, other types will be grouped by organ system affected and severity) Partial/ unclear = >=1 secondary outcomes (listed in OUR protocol) were reported No = None of the outcomes listed in OUR protocol were reported.	Yes
	Partial/ unclear
	No
Were the relevant outcome measures made before and after the intervention? Yes = The relevant outcome measures were made pre- and post-intervention; or the baseline measurements were not possible (ex. death). Partial/ unclear = The study did not report when the outcome measures were made. No = The outcome measures were only made post-intervention.	Yes
	Partial/ unclear

	No
The study does not perform selective outcome reporting. Yes = The study protocol is registered and all of the study's pre-specified outcomes of interest were stated in the methods section. Partial/ unclear = Either study protocol registered or the study's pre-specified outcomes of interest were stated in the methods section. No = No study protocol registered and none of the study's pre-specified outcomes of interest were stated in the methods section.	Yes
	Partial/unclear
	No
Were details of the statistical tests reported? Yes = The statistical tests were reported in the study. Partial/unclear = Statistical tests only partially described or reported elsewhere (e.g previous paper, or protocol). No = The statistical tests were not described in the study. N/A = N of 1 study.	Yes
	Partial/unclear
	No
	N/A
Was follow-up period reported? Yes = follow-up information was reported. No = Length of follow-up was not reported.	Yes
	No
Did the study provide estimates of random variability in the data analysisof relevant outcomes? Yes = Estimates of the random variability (ex. SE, SD, CI) were reported for all relevant outcomes and/or could be calculated from the raw data. Partial/ unclear = Estimates if the random variability were reported for some, but not all relevant outcomes. No = Estimates of the random variability were not reported for any of the relevant outcomes. N/A = N of 1 study.	Yes
	Partial/unclear
	No
	N/A
Were the adverse events reported? Includes: Infection, neurotoxicity, cytokine release syndrome, B-cell aplasia, and graft versus host disease. Yes = All adverse events were reported. Partial/ unclear = Unclear if all the adverse events were reported. No = No information about adverse events reported.	Yes
	Partial/ unclear
	No

Were both competing interests and sources of support for the study reported? Yes = Both competing interests and sources of support (financial or other) received for the study were reported; or the absence of support was acknowledged. Partial/ unclear = Either the competing interest or source of support was reported. No = Neither competing interests nor sources of support were reported.	Yes
	Partial/ unclear
	No

Appendix 3. Contributor roles taxonomy

Contributor Role[1]	Role Definition
Conceptualization	Ideas; formulation or evolution of overarching research goals and aims.
Data Curation	Management activities to annotate (produce metadata), scrub data and maintain research data (including software code, where it is necessary for interpreting the data itself) for initial use and later reuse.
Formal Analysis	Application of statistical, mathematical, computational, or other formal techniques to analyze or synthesize study data.
Funding Acquisition	Acquisition of the financial support for the project leading to this publication.
Investigation	Conducting a research and investigation process, specifically performing the experiments, or data/evidence collection.
Methodology	Development or design of methodology; creation of models
Project Administration	Management and coordination responsibility for the research activity planning and execution.
Resources	Provision of study materials, reagents, materials, patients, laboratory samples, animals, instrumentation, computing resources, or other analysis tools.
Software	Programming, software development; designing computer programs; implementation of the computer code and supporting algorithms; testing of existing code components.
Supervision	Oversight and leadership responsibility for the research activity planning and execution, including mentorship external to the core team.
Validation	Verification, whether as a part of the activity or separate, of the overall replication/reproducibility of results/experiments and other research outputs.
Visualization	Preparation, creation and/or presentation of the published work, specifically visualization/data presentation.
Writing – Original Draft Preparation	Creation and/or presentation of the published work, specifically writing the initial draft (including substantive translation).
Writing – Review & Editing	Preparation, creation and/or presentation of the published work by those from the original research group, specifically critical review, commentary or revision – including pre- or post-publication stages.

[1]Author contributions based on contributor role taxonomy defined previously by Brand *et al.* (50)

PRISMA-P 2015 Checklist

This checklist has been adapted for use with systematic review protocol submissions to BioMed Central journals from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

An Editorial from the Editors-in-Chief of *Systematic Reviews* details why this checklist was adapted - Moher D, Stewart L & Shekelle P: Implementing PRISMA-P: recommendations for prospective authors. *Systematic Reviews* 2016 **5**:15

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	4
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	2
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	20-21
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☒	☐	19
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	18-20
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	18-20
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☒	☐	20
INTRODUCTION					

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	4-6
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	8
METHODS					
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	7-8
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	9
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	9
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	10
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	10
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	10
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	10-11
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	12-15
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	15-16
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	16-17
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of	☒	☐	16-17

Section/topic	#	Checklist item	Information reported		Page number(s)
			Yes	No	
		consistency (e.g., I^2, Kendall's tau)			
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	17
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	16-17
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	16
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	18